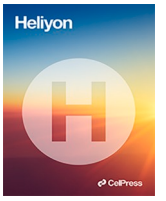
Heliyon 10 (2024) e26773

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Aortic arch blood flow measurements as a predictor of successful ECMO weaning in cardiogenic shock

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ARTICLE INFO

Keywords:
ECMO
Cardiogenic shock
Weaning
Aortic arch
Doppler ultrasound
USCOM

ABSTRACT

Objective: Acute cardiogenic shock is a life-threatening condition with mortality rates of up to 50%. If conventional therapy fails, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) therapy has emerged to a promising alternative for temporary cardiac and respiratory support in specialized centers. However, it is only a bridge to recovery, final decision, heart transplantation or the permanent implantation of a left ventricular assist device. Therefore, the identification of the optimum weaning time point is challenging, and standardized weaning protocols are rare.

Methods: In this explorative pilot study, we evaluated the potential benefit of blood flow measurements in the aortic arch using an ultrasonic cardiac output monitor (USCOM) for the primary endpoint of successful VA-ECMO weaning. 12 patients under VA-ECMO therapy for acute cardiogenic shock and a hemodynamic condition which qualified for a stepwise weaning process were included in this study. Main exclusion criterion was the presence of additional venting therapy for left ventricular unloading, e.g. Impella. Statistical comparisons were performed using the Mann-Whitney test and corrected for multiple testing by the Holm-Sidak method.

Results: Peak velocity of flow in the aortic arch showed a positive correlation with weaning success independent of ECMO flow (weaning success vs. failure: 0.75 vs. 0.35 m/s (low ECMO support), $p = 0.049$), whereas we identified only a trend for mean pressure gradient, minute distance and stroke volume index.

Conclusion: We hypothesize, that USCOM might provide an additive benefit to conventional strategies in its ability to predict successful VA-ECMO weaning and prevent pulmonary congestion. Larger upcoming trials are required to address this relevant topic and provide standardized treatment protocols for optimized weaning in the future.

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https://doi.org/10.1016/j.heliyon.2024.e26773
Received 11 July 2023; Received in revised form 8 December 2023; Accepted 20 February 2024
Available online 23 February 2024

Abbreviations

VA	Veno-arterial
ECMO	Extracorporeal membrane oxygenation
LV	Left ventricle
LVEF	Left ventricular ejection fraction
USCOM	Ultrasonic cardiac output monitor
IABP	Intra-aortic balloon pump
VTI	Velocity time integral
IQR	Interquartile range
SOFA	Sequential organ failure assessment
SAPS	Simplified acute physiology score
PEEP	Positive end-expiratory pressure
NA	Noradrenalin
SUPRA	Suprarenin
DOBU	Dobutamine
RR	Blood pressure
Sys	Systolic
Dia	Diastolic
PP	Pulse pressure
SV	Stroke volume
SVI	Stroke volume index
CO	Cardiac output
CI	Cardiac index
Vpk	Peak velocity of flow
Pmn	Mean pressure gradient
MD	Minute distance
ET	Ejection time
FT	Flow time
PiCCO	Pulse contour cardiac output
CPR	Cardiopulmonary resuscitation

1. Introduction

Acute cardiogenic shock is a life-threatening emergency associated with high mortality rates. Common treatment strategies are mainly based on volume management, high-dose inotropes and vasopressors as well as mechanical ventilation. Nevertheless, this therapy remains insufficient in some cases and patients die despite all efforts [1–3].

In recent years, alongside other devices for circulatory support VA-ECMO therapy has increasingly established itself as a promising alternative. This highly complex treatment is performed in specialized centers and provides temporary cardiac and respiratory support [4,5]. However, overall mortality rates remain high, ranging between 40 and 50%, and potential vascular complications as well as relevant effects on hemostasis should not be neglected [1,6,7].

As VA-ECMO is only a bridge to recovery, final decision, heart transplantation or persistent mechanical circulatory support, weaning of this temporary treatment strategy is a step of fundamental importance [8]. Identifying the optimal timing for ECMO weaning remains a significant challenge and standardized protocols are still lacking [9,10]. Additionally, many patients in severe cardiogenic shock develop a significant respiratory failure due to pulmonary congestion. This is due to a relevant countercurrent of blood in the aortic arch, which leads to an increased afterload. Therefore, antegrade blood flow through the aortic valve is restricted, while at the same time cardiac contractility recovers. Current strategies for afterload reduction involve mainly the use of the intra-aortic balloon pump (IABP), the coaxial pump Impella that transfers blood from the left ventricle (LV) into the aorta for left ventricular unloading as well as optimized weaning approaches. Finding the right time for gradual weaning and eventual removal of ECMO remains crucial in circulatory support therapy [9]. Furthermore, determination of cardiac output in the setting of VA-ECMO is challenging. Diagnostic techniques like oxygen saturation measurements (for Fick equation calculations) or thermodilution are limited or even not feasible due to the countercurrent and changes in pressure, oxygenation and temperature under circulatory support.

A limited number of studies investigated transthoracic ultrasound-assisted strategies for assessment of cardiac output and weaning. They identified the following parameters as valid predictors of weaning success: left ventricular ejection fraction (LVEF), contractility parameters on the mitral and tricuspid valve level (mitral lateral e' velocity, mitral/tricuspid annular S′ velocity) as well as an aortic velocity time integral (VTI) > 10 cm [11–13]. Yet, transthoracic ultrasound of the heart in intensive care patients in the supine position is difficult and often time-consuming. Moreover, results of cardiac flow velocity measurements are limited when intracardiac LV venting devices are use simultaneously.

Aortic arch Doppler ultrasound examinations are performed with an ultrasonic cardiac output monitor (USCOM) which was

previously validated for cardiac output calculations [14]. As a non-invasive and efficient tool, USCOM offers potential in overcoming the limitations of existing monitoring methods, a hypothesis our study aims to explore. The measurement of pulsatile antegrade flow in the aortic arch as well as indirect parameters of the prevailing laminar countercurrent might help to optimize ECMO weaning strategies, and at the same time to identify parameters that best prevent the development of pulmonary congestion.

2. Materials and methods

2.1. Patients

From February 2021 to June 2023, we prospectively enrolled 12 patients under circulatory support with VA-ECMO due to acute cardiogenic shock refractory to conservative shock therapy including volume substitution and catecholamine therapy. Inclusion criteria were a hemodynamic situation, which qualified for stepwise ECMO weaning according to our institutional protocol [9] and a minimum ECMO therapy duration of 3 days to allow reliable calculations. We excluded patients with additional venting therapy for LV unloading or those with other systems for mechanical circulatory support, e.g. Impella or IABP.

All patients were treated in the cardiac intensive care unit (ICU) of Ludwig-Maximilians-University hospital (Munich, Germany) and participated in the LMUshock registry. The latter is registered at the WHO International Clinical Trials Registry Platform (DRKS00015860) and was approved by the local ethics committee (approval number: 18-001). It contains our local ICU patients admitted with acute cardiogenic shock as well as those after successful cardiopulmonary resuscitation. USCOM measurements were carried out as part of our clinical routine independent of study participation. Informed consent was obtained from all survivors after recovery. The study was conducted in accordance with the Declaration of Helsinki and German data protection laws.

2.2. Study endpoint

The study endpoint of this pilot study was successful VA-ECMO weaning, defined in line with previous studies as not requiring further mechanical circulatory support within 30 days after VA-ECMO removal [15,16].

2.3. Data collection

USCOM 1A (Uscom, Australia) measurements were collected on day 2 ± 1 under high (>4 l/min) and low (2-2,5 l/min) ECMO flow settings which were maintained for at least 10 min prior to data acquisition. Additionally, we collected hemodynamic and respiratory parameters as well as baseline data from patient records as indicated.

2.4. Illustrations

The graphical illustrations of the USCOM evaluation set-up during VA-ECMO therapy was designed with the help of Adobe Illustrator 2021 (Adobe, USA).

2.5. Statistical analyses

Statistical analyses were performed using GraphPad Prism 9 (GraphPad Software, USA). Continuous variables are presented as median (interquartile range, IQR) and categorical variables as % (n). Weaning groups were compared using the Mann-Whitney test and corrected for multiple comparisons by the Holm-Sidak method. Adjusted p-values <0.05 were rated as statistically significant.

3. Results

3.1. Characteristics of the study population

12 patients requiring VA ECMO therapy due to refractory acute cardiogenic shock were included. Median age of the predominantly male cohort (11/12) was 58.0 (54.6; 61.4) years with a slightly elevated body mass index of 26.3 (24.4; 29.6) kg/m^2. In 83% of all cases, patients were admitted after sudden cardiac arrest and subsequent cardiopulmonary resuscitation (CPR). The underlying diseases were acute myocardial infarction in a majority of 6 cases, while other conditions included myocarditis (2), ventricular tachycardia storm (1), pulmonary embolism (1) or exacerbated forms of a preexisting cardiomyopathy (2) (Supplementary Table 1).

The investigated cohort was subdivided according ECMO weaning outcome (7/12 success (+); 5/12 failure (−)). Despite of the limited number of cases preexisting major disease and cardiovascular risk factors were similarly distributed between the two groups. The successful weaning group included 4 patients with known coronary artery disease, a preexisting pulmonary disease, a previous intracranial bleeding as well as a history of cancer was known in one patient. In the weaning failure group 5 patients had known coronary artery disease and two patients had a previous intracranial bleeding. Both groups included 4 individuals with chronic kidney disease. Median ECMO therapy duration was 120 h in both cohorts ((+) vs. (−): 120 (108; 192) vs. 120 (120; 120), $p > 0.99$) (Supplementary Table 1).

3.2. Parameters of organ function

Basic assessment scores of organ function and physiology such as sequential organ failure assessment (SOFA) (10 (4.0; 13.0) (+) vs. 10.0 (9.0; 14.5) (−); $p > 0.99$) or simplified acute physiology score (SAPS) (56.0 (49.0; 71.0) (+) vs. 57.0 (47.0; 59.0) (−); $p > 0.99$) were similar irrespective of weaning success. Moreover, also respiratory parameters, including FiO2 and pressure levels, did not show any difference between the two cohorts (Table 1). Regarding cardiac function parameters, we observed only very mild non-significant differences with respect to a reduced left ventricular ejection fraction (LVEF), as well as higher doses of catecholamines and lactate levels in the weaning failure group (Table 1).

3.3. Aortic arch blood flow measurements using USCOM

High VA-ECMO flow was 4.14 (4.10; 4.18) l/min at 2815 (2757; 2873) rpm, whereas low VA-ECMO flow translated to 2.36 (2.26; 2.45) l/min at 1954 (1801; 2106) rpm. Median heart rate was independent of ECMO flow or weaning success between 69 and 81 bpm (high ECMO support: 77 (73; 81) bpm; low ECMO support 78 (75; 81) bpm). While median blood pressure was similar in the positive and negative ECMO weaning group (low ECMO support: 64 (61; 70) (−) vs. 72 (65; 82) (+); adjusted $p = 0.289$), we observed significantly higher values of systolic blood pressure and a non-significant trend for pulse pressure (low ECMO support: RRsys (mmHg) 85.0 (65.0; 94.5) (−) vs. 108.0 (104.0; 122.0) (+); $p = 0.049$, PP (mmHg) 30.0 (7.5; 38.0) (−) vs. 51.0 (39.0; 62.0) (+); $p = 0.029$) in the successful weaning group as surrogate for cardiac contractility (Fig. 1, Table 2). This is also reflected by a trend towards higher calculated values of stroke volume index and cardiac index according to non-invasive USCOM measurements. Interestingly, this difference was detected under low as well as high levels of ECMO support (Fig. 1, Table 2). Peak velocity of flow (vpk) was lower in the ECMO weaning failure group (low ECMO support: 0.35 (0.34; 0.55) (−) vs. 0.75 (0.63; 0.80) m/s (+); $p = 0.049$; high ECMO support 0.34 (0.32; 0.46) (−) vs. 0.69 (0.57; 0.81) m/s (+); $p = 0.044$). Similarly, however non-significant, the minute distance (MD), i.e. the distance which blood travels in 1 min (normal values: 14–22 m/min), was about twice as high in the successful weaning group as an indicator of cardiac contractility (low ECMO support: 5.60 (4.95; 9.85) (−) vs. 10.50 (7.30; 11.00) m/min (+); $p = 0.59$). Of note, the ECMO countercurrent noticeably restricted MD in line with an increase in cardiac afterload (high ECMO support 2.60 (2.10; 5.25) (−) vs. 8.10 (5.30; 9.90) m/min (+); $p = 0.060$). Also, the relative ejection time (ET, %) and the absolute flow time (FT, ms) were negatively affected by the countercurrent as expected (Fig. 1, Table 2).

4. Discussion

In this pilot study we correlated flow patterns in the aortic arch with weaning success in the setting of VA-ECMO therapy. Although we identified no clear association between ECMO flow parameters, cardiac function and pulmonary congestion, our measurements showed highly interesting results in terms of optimized ECMO weaning strategies and cardiac output determination.

In line with previous studies, we identified systolic blood pressure and pulse pressure as a useful surrogate for cardiac contractility and weaning success [17,18]. As a marker for overall perfusion and general organ function serum lactate levels were also identified as a good predictor of successful ECMO weaning in previous studies [9]. However, lactate values show a high variation and underly multiple confounders such as systemic infections or preexisting comorbidities and did not reach significance in our present pilot study.

Table 1
Parameters of organ function at USCOM measurement.

		Weaning outcome	
	Total (n = 12)	Success (n = 7)	Failure (n = 5)
FiO2	0.54 (0.49; 0.59)	0.45 (0.35; 0.65)	0.55 (0.50; 0.70)
Respiratory rate (/min)	15.6 (15.0; 16.1)	16.0 (15.0; 18.0)	16.0 (11.5; 18.0)
Peak ventilation pressure (mmH_20)	23.9 (22.9; 25.0)	22.0 (22.0; 24.0)	26.0 (21.5; 28.0)
PEEP (mmH_20)	11.8 (11.0; 12.6)	12.0 (10.0; 12.0)	13.0 (11.0; 14.0)
LVEF measurement (%)	18.4 (16.0; 20.7)	20.0 (20.0; 20.0)	15.0 (10.0; 22.5)
NA measurement (μg/kg/min)	0.14 (0.04; 0.24)	0.02 (0.00; 0.08)	0.514 (0.03; 0.51)
SUPRA measurement (μg/kg/min)	0.01 (0.00; 0.02)	0.00 (0.00; 0.00)	0.00 (0.00; 0.06)
DOBU measurement (μg/kg/min)	2.83 (1.85; 3.80)	1.85 (0.00; 3.33)	4.17 (1.90; 5.52)
Lactate measurement (mmol/l)	1.87 (1.44; 2.30)	1.3 (1.3; 1.7)	2.2 (1.1; 3.6)
SOFA score measurement	10.6 (9.7; 11.4)	10.0 (4.0; 13.0)	10.0 (9.0; 14.5)
SAPS measurement	56.7 (53.8; 59.6)	56.0 (49.0; 71.0)	57.0 (47.0; 59.0)
LVEF admission (%)	19.5 (19.0; 20.0)	20.0 (20.0; 20.0)	20.0 (12.5; 25.0)
LVEF discharge (%)	26.9 (16.0; 37.9)	45.0 (20.0; 55.0)	15.0 (10.0; 22.5)
NA max (μg/kg/min)	0.43 (0.39; 0.47)	0.25 (0.21; 0.55)	0.50 (0.23; 0.68)
SUPRA max (μg/kg/min)	0.02 (0.01; 0.04)	0.00 (0.00; 0.00)	0.00 (0.00; 0.09)
DOBU max (μg/kg/min)	3.71 (3.41; 4.02)	3.70 (2.38; 4.17)	4.17 (1.90; 5.52)
Lactate max (mmol/l)	9.4 (7.4; 11.4)	4.1 (2.5; 17.0)	15.0 (3.5; 17.5)

All variables are presented as median (IQR). Comparisons between groups were non-significant for all presented variables. PEEP, positive end-expiratory pressure; LVEF, left ventricular ejection fraction; NA, noradrenalin; SUPRA, suprarenin; DOBU, dobutamine; SOFA, sequential organ failure assessment; SAPS, simplified acute physiology score.

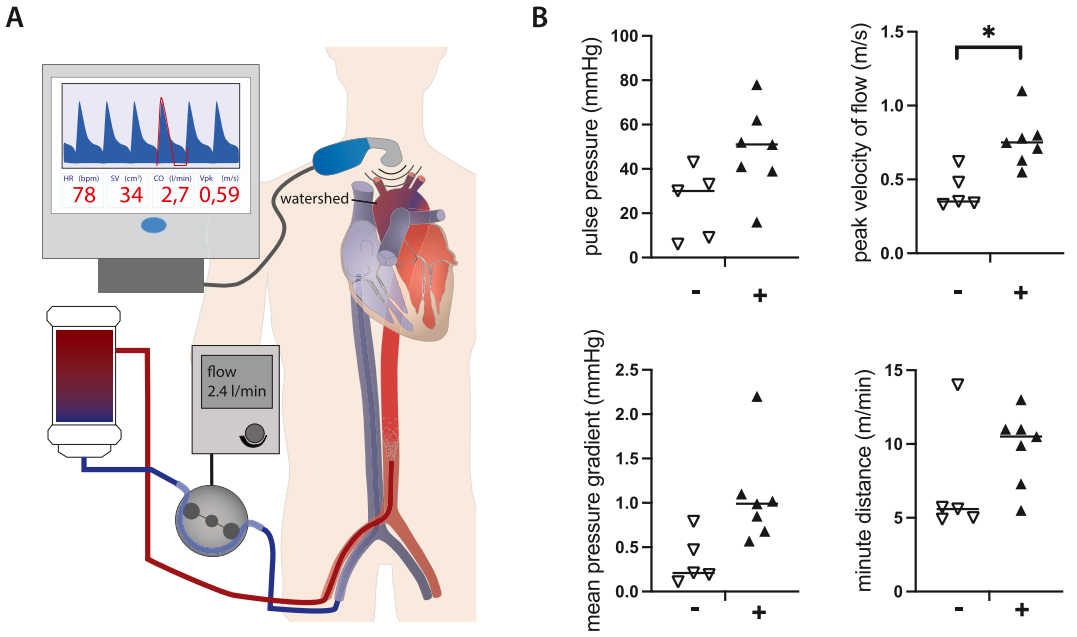

Fig. 1. USCOM-guided ECMO weaning. (A) Depicted are schematic graphs of USCOM measurements during ECMO therapy under low flow conditions. (B) Graphical illustration of major USCOM parameters in the negative (−) and positive (+) weaning group under low flow conditions.

Table 2
USCOM parameters.

		ECMO weaning outcome			
High ECMO flow 4.14 (4.10; 4.18) l/min	**Total (n = 12)**	**Success (n = 7)**	**Failure (n = 5)**	**P value**	**Adjusted p value**
RRsys (mmHg)	96.1 (82.0; 110.3)	111.0 (99.0; 117.0)	89.0 (69.5; 91.0)	0.003	0.025
RRdia (mmHg)	62.3 (61.8; 62.7)	60.0 (57.0; 67.0)	60.0 (55.5; 69.0)	>0.999	>0.999
PP (mmHg)	33.9 (20.2; 47.6)	50.0 (40.0; 54.0)	20.0 (5.5; 35.0)	0.016	0.060
SVI (ml/m^2)	12.1 (9.3; 14.9)	15.0 (11.0; 16.0)	9.1 (7.7; 11.0)	0.009	0.060
CI (l/min/m^2)	0.85 (0.52; 1.18)	1.20 (0.84; 1.50)	0.45 (0.28; 0.80)	0.010	0.060
Vpk (m/s)	0.54 (0.38; 0.71)	0.69 (0.57; 0.81)	0.34 (0.32; 0.46)	0.005	0.045
Pmn (mmHg)	0.66 (0.31; 1.01)	0.97 (0.61; 1.20)	0.25 (0.24; 0.41)	0.005	0.045
MD (m/min)	5.59 (3.46; 7.73)	8.10 (5.30; 9.90)	2.60 (2.10; 5.25)	0.010	0.060
ET (%)	23.4 (16.0; 30.9)	32.0 (19.0; 41.0)	16.5 (13.8; 17.8)	0.015	0.060
FT (ms)	222.7 (215.0; 230.4)	210.0 (160.0; 310.0)	215.0 (182.5; 247.5)	>0.999	>0.999
		ECMO weaning outcome			
Low ECMO flow 2.36 (2.26; 2.45) l/min	**Total (n = 12)**	**Success (n = 7)**	**Failure (n = 5)**	**P value**	**Adjusted p value**
RRsys (mmHg)	95.1 (80.8; 109.4)	108.0 (104.0; 122.0)	85.0 (65.0; 94.5)	0.005	0.049
RRdia (mmHg)	58.8 (56.6; 61.0)	60.0 (56.0; 69.0)	58.0 (53.5; 59.0)	0.372	0.753
PP (mmHg)	36.3 (24.2; 48.4)	51.0 (39.0; 62.0)	30.0 (7.5; 38.0)	0.048	0.291
SVI (ml/m^2)	16.3 (13.8; 18.9)	19.0 (13.0; 27.0)	13.0 (11.0; 17.0)	0.164	0.592
CI (l/min/m^2)	1.28 (1.07; 1.49)	1.50 (1.00; 1.90)	0.86 (0.80; 1.44)	0.081	0.400
Vpk (m/s)	0.59 (0.42; 0.76)	0.75 (0.63; 0.80)	0.35 (0.34; 0.55)	0.005	0.049
Pmn (mmHg)	0.71 (0.35; 1.06)	0.99 (0.68; 1.10)	0.21 (0.15; 0.63)	0.010	0.078
MD (m/min)	8.39 (7.04; 9.74)	10.50 (7.30; 11.00)	5.60 (4.95; 9.85)	0.188	0.592
ET (%)	38.3 (36.1; 40.5)	37.0 (24.0; 45.0)	41.5 (28.5; 51.5)	0.494	0.753
FT (ms)	283.8 (272.6; 295.0)	310.0 (200.0; 330.0)	295.0 (260.0; 330.0)	0.927	0.927

All variables are presented as median (IQR). P values were calculated using the Mann-Whitney test and adjusted for multiple comparisons by the Holm-Sidak method. RRsys, systolic blood pressure; RRdia, diastolic blood pressure; PP, pulse pressure; SV, stroke volume; SVI, stroke volume index; CO, cardiac output; CI, cardiac index; Vpk, peak velocity of flow; Pmn, mean pressure gradient; MD, minute distance; ET, ejection time; FT, flow time.

LVEF was clearly impaired with 18.4% (16.0; 20.7) in all our patients after two days of ECMO therapy. We did not detect any significant differences in relation to weaning success (LVEF: 15.0 (10.0; 22.5) (−) vs. 20.0 (20.0; 20.0) % (+); p = 0.97). Yet, we observed a numerical trend to slightly higher LVEF values in the successful weaning group. This observation was also reported in preceding studies on transthoracic ultrasound-guided weaning, where critical LVEF cutoff values of 20%–33% were reported [11–13].

However, transthoracic echocardiography is often limited in supine position under mechanical ventilation and even more when an additional Impella device is present for LV unloading.

The evaluation of hemodynamics has strong limitations under ECMO therapy and pulmonary catheters, including calculations based on the thermodilution method, as well as pulse contour cardiac output (PiCCO) measurements cannot be used in this setting. Therefore, central venous oxygen saturation has emerged to a standard evaluation parameter although it reflects multiple conditions beyond cardiac function [9]. Especially, pulmonary function has a strong impact, and it is usually impaired in the VA-ECMO cohort in acute cardiogenic shock. As mentioned above, echocardiographic evaluations might be limited by imaging quality and can potentially be influenced by the increased afterload under ECMO therapy. Therefore, the measurement of blood flow patterns in the aortic arch by USCOM seem to be a complementary system to evaluate parameters of cardiac contractility without major external influences [14].

Independent of the level of ECMO support, peak velocity of flow (low ECMO support: 0.35 m/s vs. 0.75 m/s; $p = 0.049$) and mean pressure gradient (low ECMO support: 0.21 (−) vs. 0.99 mmHg (+); $p = 0.078$) appeared to be a good surrogate of cardiac function and subsequent successful weaning. Other values such as calculated cardiac output or stroke volume also seem to correlate with weaning success but did not reach significance, which might be due to the limited sample size of our pilot study cohort. Additionally, we must keep in mind, that these latter numerical values might not reflect proper measurements as USCOM calculations were not evaluated for these conditions under VA-ECMO therapy.

The impact of a countercurrent in the aorta, potentially leading to cardiac overload and pulmonary congestion, can be evaluated simultaneously. In line with this ET, FT, vpk and MD were dependent on the level of ECMO support.

Our pilot study has several limitations: just as with ultrasound imaging, the USCOM measurement is dependent on the examiner, which might lead to non-predictable deviations in cardiac output monitoring. Larger patient cohorts are required to compensate for these potential aberrations. Still, the USCOM technique is fast and feasible and promises a rapid learning curve. Furthermore, the study population was small and heterogenous. In the setting of critical care various etiologies can demand mechanical support and our measurement was only conducted at one specific time point and not throughout the course of the disease. Further data on the ideal time point of USCOM measurements is required to optimize ECMO weaning guidance. The fact that our cohort is predominantly male, is in line with the data from large randomized controlled trials on patients with acute cardiogenic shock and can probably be attributed to a higher corresponding cardiovascular risk profile [1–3].

In conclusion, USCOM measurements might be a very useful tool to identify the optimum time point of successful ECMO weaning and prevent pulmonary congestion along with increasing contractility of the LV. It should not be regarded as an alternative, but rather supplemental to conventional transthoracic echocardiography and other tools of successful weaning prediction. The add-on value of USCOM measurements should now be evaluated in larger trials to provide potential optimized ECMO weaning strategies for the future and evaluate the optimal time point of USCOM measurements. Furthermore, we should identify patient cohorts that benefit the most from USCOM measurements beyond those addressed in our pilot study. Potential applications could be patient cohorts under VA-ECMO therapy for protected percutaneous interventions, after cardiac surgery or in combination with other mechanical circulatory support devices.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

Data will be made available on request.

Ethics statement

This study was reviewed and approved by the institutional ethics committee of Ludwig-Maximilians-University hospital (Munich, Germany), with the approval number: 18-001.

CRediT authorship contribution statement

Antonia Kellnar: Writing – review & editing, Writing – original draft, Visualization, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Dominik Naumann:** Writing – review & editing, Validation, Formal analysis. **Clemens Scherer:** Writing – review & editing, Validation, Resources, Formal analysis. **Enzo Lüsebrink:** Writing – review & editing, Validation, Formal analysis. **Dominik Joskowiak:** Validation, Resources. **Sven Peterß:** Validation, Resources. **Christian Hagl:** Writing – review & editing, Validation, Resources. **Steffen Massberg:** Writing – review & editing, Validation, Supervision, Resources. **Martin Orban:** Validation, Supervision, Resources, Investigation. **Christopher Stremmel:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e26773.

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